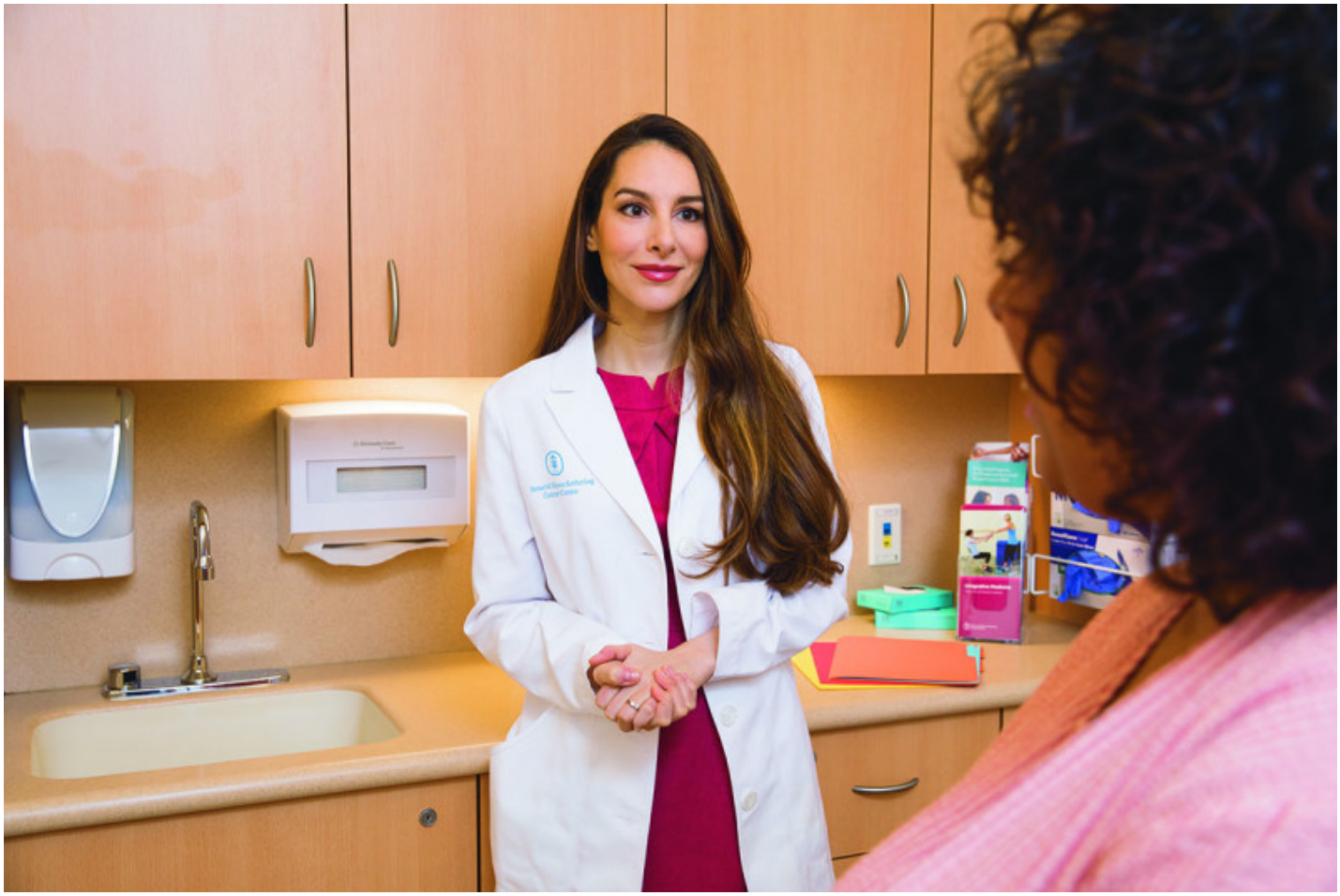
What Causes Leukemia after Breast Cancer? Research Shows That a Mutation May Be Present All Along

By Julie Grisham, **Monday, September 9, 2019**



Medical oncologist Elizabeth Comen led a study that revealed new details about how and when secondary leukemias may originate after breast cancer.

Summary

A new study from Memorial Sloan Kettering suggests that in some people treated for breast cancer, leukemia-causing gene mutations may be present in blood cells from the time the original cancer was diagnosed. This helps explain some cases of secondary leukemia.

Doctors have known for a long time that cancer survivors may be at risk of a rare aftershock: developing a secondary **leukemia** years or even decades later. Because some chemotherapy drugs can damage the DNA in the bone marrow, where leukemia forms, experts have assumed that the drugs trigger the formation of cancerous blood cells that lead to leukemia.

A new study of people with **breast cancer** treated at Memorial Sloan Kettering is turning that idea on its head. The findings suggest that in some people, leukemia-causing gene mutations may be present in blood cells from the time that breast cancer is originally diagnosed, before chemotherapy is ever given. Although this discovery is important, the study looked at only a small group of patients, so larger studies are needed to confirm the findings.

"In the past, we've never been able to predict which breast cancer patients may be at risk for developing leukemia in the future," says medical oncologist **Elizabeth Comen**, first author of the **study** published August 27 in the *Journal of the National Cancer Institute* (*JNCI*). "Our findings provide new clues about how and when these leukemias may originate. They also suggest that we may be able to identify who is at risk of developing leukemia, paving the way to prevent secondary leukemias."

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Elizabeth Comen
medical oncologist

About 70% of secondary leukemias occur in people who have been treated for breast cancer. (The rest are in people treated for other types of cancer, mostly other solid tumors.) Around 0.5% of people treated for breast cancer eventually develop a secondary leukemia.

Searching for a Change in the Blood

The investigators focused on seven women treated for breast cancer at MSK who later developed a specific type of leukemia called **acute myeloid leukemia**. They studied the original tumor tissue that was removed at the time of surgery to look for signs of cancer in the blood. They focused on white blood cells, a component of the immune system, which are often present in the environment surrounding tumor cells.

"In four of the seven women who went on to develop leukemia, we could detect cancer-causing mutations in the immune cells that were removed with their original tumors," says physician-scientist **Ross Levine**, senior author of the study. "Previous studies have reported cases in which leukemia mutations were observed years before people with solid tumors developed therapy-related leukemia. We were able to show that in many cases, secondary leukemia arises because preexisting altered blood cells are already there at the time of the first cancer."

The changes observed in the immune cells are due to a phenomenon called clonal hematopoiesis (CH), **which Dr. Levine studies**. People with CH have an increased number of white blood cells that carry mutations that are also found in blood cancers. Some people with CH will go on to develop leukemia, although most do not.

"CH mutations are part of aging," Dr. Comen says. "You can think of them like gray hairs or wrinkles but in the immune system." Studies have suggested that between 10 and 20% of people over age 70 have signs of CH in their blood.

A Unique Collaboration

The *JNCI* study came about because of a unique collaboration among members of MSK's Breast Medicine Service, Leukemia Service, and Department of Pathology. Physician-scientist **Jorge Reis-Filho**, Chief of the Experimental Pathology Service and an expert in uncovering detailed molecular information from archival tumor samples, was another co-author on the study.

Dr. Reis-Filho used a lab technique called laser capture microdissection (LCM) to separate immune cells from tumor cells within the tumor tissue. "This technology has been around for more than a decade," he explains, "but this was the first time that we used this method to ask such an important clinical question and to define the clinical impact of mutations affecting immune cells."

Although the mutations are present much earlier than previously known, the investigators don't completely dismiss the role of chemotherapy in the development of leukemia. They believe that these drugs may make the environment for leukemia more hospitable and may help it grow and spread more effectively.

Next Steps for a Surprising Finding

Much more research needs to be done to validate these findings in a larger number of people. The investigators also plan to expand this work to look for the presence of immune cells with CH mutations in other types of solid tumors. Drs. Comen and

Reis-Filho are currently developing new ways to look for these mutations that are less labor-intensive than LCM.

According to Dr. Levine, there are several long-term goals of this research. “Once we know who is at risk of developing leukemia, we can monitor them so we can catch the disease early. It’s also possible that these findings could influence the treatment that patients get for their initial cancer,” he says. “Ultimately, we hope this research will lead to ways to prevent or reverse the progression from CH to leukemia.”

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Ross L. Levine
physician-scientist

These efforts are all part of a larger push in CH research across MSK under the Precision Interception and Prevention Program, which is led by **Luis Diaz**, Head of the Division of Solid Tumor Oncology.

“This study — of breakthrough potential — is a great example of the kind of science that can only be accomplished by a dedicated multidisciplinary team melding laboratory expertise and clinical insight,” says co-author **Larry Norton**, Senior Vice President in the Office of the President of MSK and Medical Director of the Evelyn H. Lauder Breast Center.

“While this study provides key insight into how we may better predict who is at risk for a future leukemia, it is not cause for alarm. The risk of leukemia still remains exceptionally small for people with breast cancer,” Dr. Comen says. “Those who have specific concerns should speak to their doctors.”

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